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The Effects of Normobaric Hypoxia in P_{300} Performance and in the Performance of Working Memory Tasks (CPT, N-back) in Pilot Cadets with Normal and Slow Waves Screening EEGs

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Summary: Electroencephalograms (EEGs) are currently used in many countries to screen Air Force pilots candidates. The usefulness of EEG to predict the likelihood of abnormal activity during the training of cadets remains controversial. We investigated whether effects of normobaric hypoxia on P_{300} ERP and memory scanning performance are related to the existence of slow waves in the EEG records of cadet pilots. If so, the EEG could serve as a tool for cognitive assessment in candidate pilot screening. Some 30 screening EEG records were re-evaluated for the presence of slow wave activity. Cadets with positive records (N=15) and a control group (N=15) performed first, at sea level and then at a normobaric hypoxia, a) cognitive performance tasks, which were, i) Active memory (N-back) and ii) Focal attention (CPT) and b) the auditory "OddBall" behavioral task for eliciting the P_{300} evoked response. The salient finding of this study was that the focal or bilateral brief periods of slow activity in the EEG records of Hellenic air Force cadets combined with conditions of hypoxia did not affect their performance of the memory scanning tasks or their ERPs measured from the auditory “OddBall' task

Electroencephalograms (EEGs) are currently used in many countries to screen Air Force pilot candidates for epileptiform activity (spikes or spike-waves)(10). These EEG records are used as a baseline for the evaluation of brain function in the event of brain injury (10). The usefulness of EEG epileptiform activity to predict the likelihood of seizure development remains controversial (2,6,9,12). Another issue of controversy is the significance of the presence of brief periods of bilateral or focal slow activity in the form of theta (4-7.9 Hz) or delta (0-3.9 Hz) waves in these EEG records. Picard et al. showed (15) that 36% of a population of aircrew applicants had brief periods of bilateral theta

activity in their EEG and 7% had bilateral delta activity. LeTournau and Meren (9) categorized focal or generalized slowing as abnormal while King and Liske (6) commented that these EEG findings are not necessarily abnormal and must be considered on an individual basis. In the EEG literature, brief periods of slowing are considered to be in a gray area between normal variant and abnormal EEG (13,14,16). Slow wave activity with posterior predominance is considered normal in adolescents whereas in young adults is not. However the age categories are ill defined (13). The appearance of bilateral delta and theta activity is considered abnormal in the EEG of the awake adult, although the distinction is based on the total amount of slow activity in the record and is again ill defined (14). The appearance of focal slowing of the EEG is considered to be abnormal but it does not always correlate with underlying brain pathology (16).

In a recent research we investigated whether the existence of slow waves in the EEG records of cadet pilots was related to differences in their cognitive performance, as this was assessed with memory scanning task and auditory "OddBall" task. The finding of this study was that brief periods of slow activity in the EEG records did not affect the results of the performed tasks (17)

It is well known that hypoxia affects cognitive performance (5,8) and P_{300} task (1).

In this study we investigated whether effects of normobaric hypoxia on P_{300} ERP and memory scanning performance are related to the existence of slow waves in the EEG records of cadet pilots. If so, the EEG could serve as a tool for cognitive assessment in candidate pilot screening

There are studies that have shown the appearance of EEG slow wave activity when specific cognitive tasks are performed. Mizuki et al. (11) using a paired association-learning task, found that the appearance of frontal midline theta activity was correlated with the memorization and retention processes. Gundel and Wilson (4) using topographical EEG analysis showed that during the performance of memory scanning tasks there was a reduction of alpha rhythm in parietal and occipital areas and an increase in theta activity in the left frontal area. Moreover it is believed that the appearance of focal EEG slowing may be correlated to a specific functional brain impairment that cannot be detected using brain-imaging techniques (i.e. CT scan, MRI) (16). This functional brain impairment might be reflected in subtle differences of cognitive performance. A relationship between spontaneous EEG slowing in some individuals and subtle differences in the performance of cognitive tasks could exist. A simple screening EEG could provide useful information about cognitive function and could serve as a starting point for further cognitive evaluation of these individuals.

MATERIALS-METHODS

The EEG records of 29 Hellenic Air Force Academy cadets were retrieved from the archives of the Neurology Department of the Hellenic Air Force Center of Aviation Medicine. The EEG records were obtained using an 18-channel electroencephalograph (Nihon Kohden Model EEG 4317F). The 10-20 system was used for electrode placement on the skull. Recording time was approximately 20 min and the procedure included 3 min of hyperventilation and 4-5 brief periods of photostimulation. All subjects had received food 1-2 h before the examination. The EEGs were performed approximately 18mo before our testing when the cadets were medically examined after admission to the Academy. The cadets' age range at the time the EEG was obtained was 17-20 yr with a mean of 18,43 yr (standard deviation [SD] ± 0,84). All cadets were male.

The EEG records were retrospectively evaluated by three experienced neurologists and categorized as: a) normal (normal with no slow wave activity); b) Bilateral slow (bilateral brief periods of focal slow activity during rest EEG); c) Right Slow (brief periods of focal slow with right dominance); d) Left Slow (brief periods of focal slow activity with left dominance and e) undecided (the cases for which the evaluators disagreed in classification) (**Table 1**).

Normobaric Hypoxia:

Each subject was exposed acutely to normobaric hypoxia breathing through a mask a given mixture of O_2 and N_2. Percentage arterial oxyhemoglobin saturation (SaO_2) was continuously measuring at the finger tip with an infrared device, so as, through adjustments of the percentage of the mixture, the level of SaO_2=90% could always be maintained.

Groups	**EEG record**
Normal	15
Bilateral slow	8
Right slow	4
Left slow	2
Total	29

Table 1: Classification of the EEG records

Memory Scanning Task:

Cadets with positive records (N=14) and a control group (N=15) performed first at sea level and then at normobaric hypoxia:

1) Cognitive performance tasks that were:

a. Active memory (N-back). During this task the cadet should keep in his memory either letters or the position of a symbol in space and respond in a few seconds. The rule is that the subject has to compare every symbol he sees with the pre-previous symbol (2-back). (**Fig.1**). We used a PC computer and a two-key Microsoft™ mouse for the performance of the visual memory-scanning task. The subject sat comfort-ably at his preferred distance in front of a color computer monitor. The subject was instructed to place two fingers of the dominant hand on the two mouse keys. The left key was designated as a "Yes" response and the right key as a "No" response for all subjects. Subjects were instructed to make as few errors as possible and to respond as soon as possible. The time from probe presentation to response (in ms) was the subject's response time for the particular trial. The temporal sensitivity of the mouse keys was 1 ms. We allowed a maximum response time of 3 s after which the trial was classified as a "Delay error". If the subject pressed the wrong key the trial was classified as a " Wrong Response Error". Response times, errors and other trial information were saved in ASCII files for the statistical analysis.

b. Focal attention (CPT). During this task the subject should compare a 4-digit number with the previous number and respond if are the same. We also used a PC computer and a two-key Microsoft™ mouse for the performance of this task. The subject sat comfort-ably at his preferred distance in front of a color computer monitor. The subject was instructed to place one fingers of the dominant hand on the left key of the mouse. Subjects were instructed to keep continuously the key down until the shown 4-digit number was the same with the previous. Then they had to leave instantly the key and keep it down again as soon as possible

2) Auditory "OddBall" Task

We used the Nicolet Spirit™ Evoked Potential System for stimulation and recording the ERP study. In particular we used the Nicolet P300 Cognitive Response software package. The task used was the auditory version of the "OddBall" paradigm. A series of auditory stimuli (tones, 80 dB, 20 cycles, ramp at 5 cycles, Blackman Envelope) was delivered to the subject's left ear through headphones. The rare stimulus (2000 Hz) was presented at random among the frequent stimuli (500 Hz). The frequency of occurrence for the rare stimulus was 20%. The subject was instructed to count the rare stimuli silently and report their number at the end of the examination. We repeated the testing if the subject was not at least 95% accurate in his count.

We used a 2-channel recording set up. The first channel recorded the potential between an electrode at vertex (Cz) and an electrode at the left earlobe. The second recorded the potential between an electrode at the parietal midline (Pz) and an electrode at the right earlobe. The reference electrode was at the frontal polar midline (Fpz). The signals were filtered (Bessel 2nd order digital low-pass filter, SNR -13.6 dB) with a low frequency cut off at 0.1 Hz and a high frequency cut off at 30 Hz. The sensitivity of the amplifiers was set at +/- 100uV. Artifacts were rejected on line by exclusion of all trials where the waveform exceeded +/- 90 uV in amplitude. Each record was 1 s ling with 200 ms of pre-stimulus baseline recording, stimulus presentation and 800 ms of response recording. The inter-stimulus interval was 1.1 s.

The waveforms for 220-375 frequent stimuli and 45-75 rare stimuli were averaged on line for each one lf the two recording channels producing four averaged waveforms for each subject. These waveforms were stored on the controlling computer's hard disk and off line latency and amplitude measurements were obtained using cursor markers. The latency of the beginning of N1 (in ms) was the time from stimulus onset to the beginning of the first post-stimulus negative wave. The latency of N1 was the time from stimulus onset to the occurrence of the peak of the first negative wave. The amplitude of N1 was the potential difference (in uV) between the peak of the first negative wave and the baseline pre-stimulus activity. The latency of P2 was the time from stimulus onset to the occurrence of the peak of the positive was following N1. The amplitude of P2 was the potential difference between the peak of N1 and the peak of P2. The latency of the beginning of P300 was the time from stimulus onset to the beginning of the positive wave after P2. The latency of P300 was the time from stimulus onset to the occurrence of the peak of the positive wave after P2 and the amplitude of P300 was the potential difference between the peak of this positive wave and the baseline pre-stimulus activity. A P300 ERP is elicited only when the rare stimuli are presented. At least two P300 components have been identified: P3a has a more frontal distribution and is elicited when the subject is not specifically attending to the rare stimuli (automatic detection); and P3b has a parietal distribution and is related to attended rare stimuli.

The amplitude of the P300 wave increases with the decrease in the probability of occurrence of the rare stimuli and is related to task difficulty and motivation. The latency of P300 is related to the perceptual evaluation of the stimulus and is not affected by the processes of response selection and execution. The prior administration of scopolamine reduces the amplitude of P300 wave and increases its latency, thus suggesting a relationship between P300 and CNS cholinergic pathways. Suggested brain generators of the P300 ERP include the hippocampus, amygdala, and the inferior parietal lobe. It has been proposed that the P300 ERP reflects the information processing to update the context of working memory. This hypothesis has been questioned. Alternative hypotheses postulate that the P300 reflects the

closing of a behavioral epoch or that it is an after-effect of earlier negativities that reflect stimulus evaluation. Although the origin of P300 ERP and the exact mechanism of its elicitation have not been conclusively defined, this ERP has been intensively used as a tool to study human cognitive processing. Auditory stimuli in the “OddBall” behavioral task elicit the N1-P2 wave complex. This wave complex occurring prior to P300 has been correlated with physical parameters of the stimuli (e.g. intensity). Three components have been identified in the N1 latency that are related to cognitive operations (endogenous components). The most interesting for our purposes is the mismatch negativity (MMN) that is elicited when a novel stimulus is compared to a previous one. The MMN has been correlated with the short-term memorization and recall of the stimuli for the comparison process.

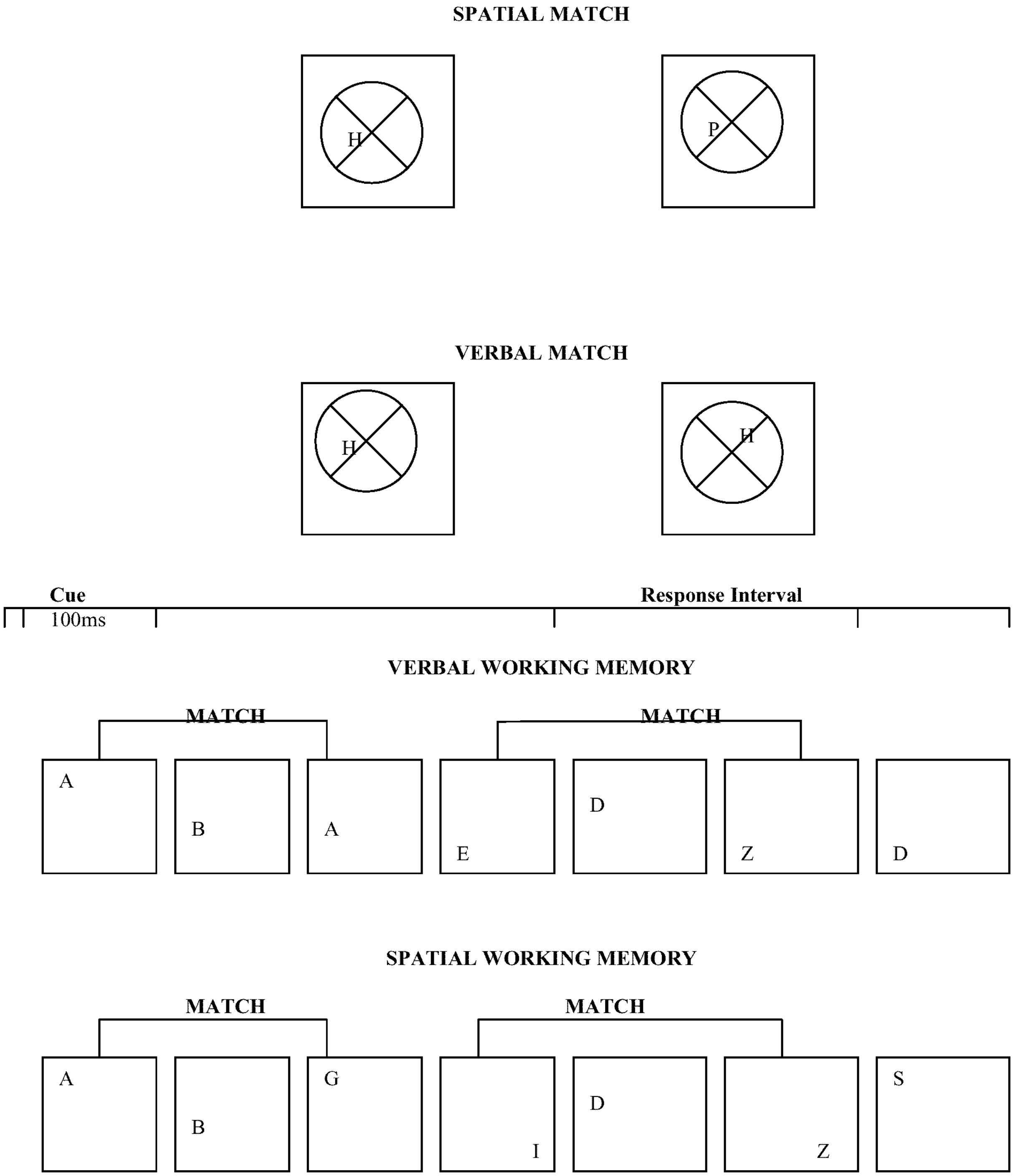


Fig.1 Schematic diagram of the course of events during the N-back task (3)

The statistical analysis of the behavioral and neurophysiological data was performed using univariate analysis of variance of SPSS 8.0 statistical package

RESULTS

1) Cognition tasks

We didn't find any statistically significant effect of the interaction of hypoxia and non-specific EEG abnormality (**Table 2**).

Factor Studied	Non-specific EEG abnormality (F stat.)	Hypoxia Effect (F stat.)	Interaction (F stat.)
Verbal N-back d'-prime	4.53*	0.29	0.55
Verbal N-back False alarms	4.355*	0.549	0.753
Verbal N-back Log Beta	0.38	4.27*	0.06
Spatial N-back d'-prime	6.7*	0.18	0.02
Spatial N-back Hits	5.968*	0.071	0.547
Spatial N-back Misses	5.658*	0.003	0.766
Spatial N-back Log Beta	0.000	0.003	0.4
CPT d'-prime	0.04	0.16	2.9
CPT Log Beta	2.56	0.86	0.02
P300 Latency	0.28	1.13	0.43

*= $p<0.05$

Table 2

A statistical significant association was found between Verbal N-back d'-prime and non-specific EEG abnormality (**Table 2** and **Fig. 2**). The subjects with normal EEGs made better scores presenting statistically significant less false alarms (**Table 2** and **Fig. 3**).

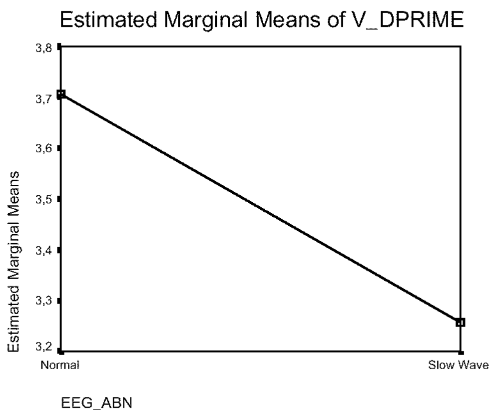


Fig. 2

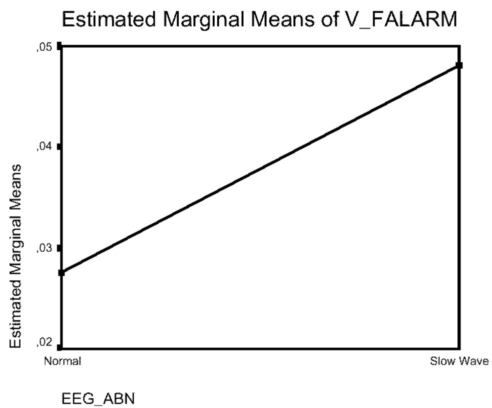


Fig. 3

A statistical significant association was found between Spatial N-back d'-prime and non-specific EEG abnormality, but in the opposite way. The subjects with "abnormal" EEGs made better scores (**Table 2** and **Fig. 4**), presenting statistically significant statistically more hits (**Table 2** and **Fig. 5**) and less misses (**Table 2** and **Fig. 6**)

The statistically significant effect of hypoxia was concerning the Verbal N-back Log Beta scores (**Table 2** and **Fig. 7**), which presents the level of taken risk. This result is in order with the early symptoms of hypoxia concerning euphoria and increased self-confidence

Fig. 4

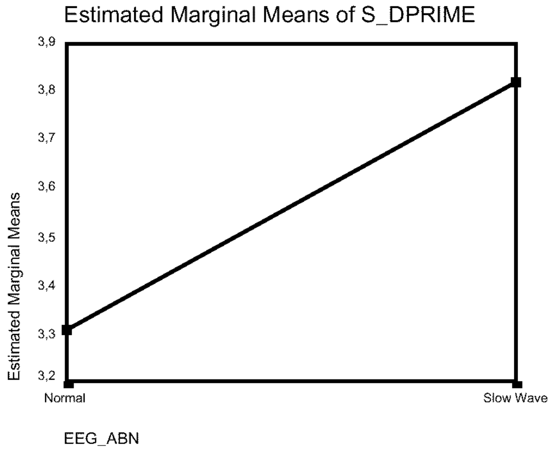


Fig. 5

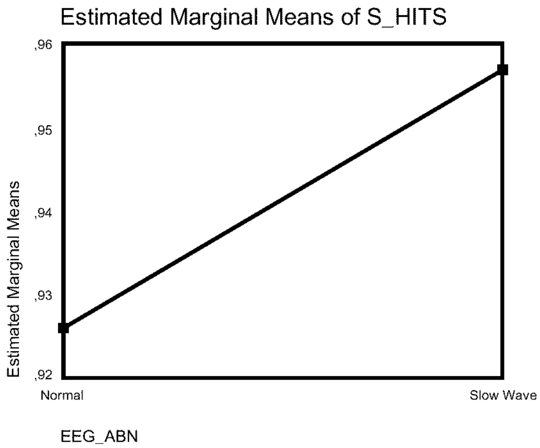


Fig. 6

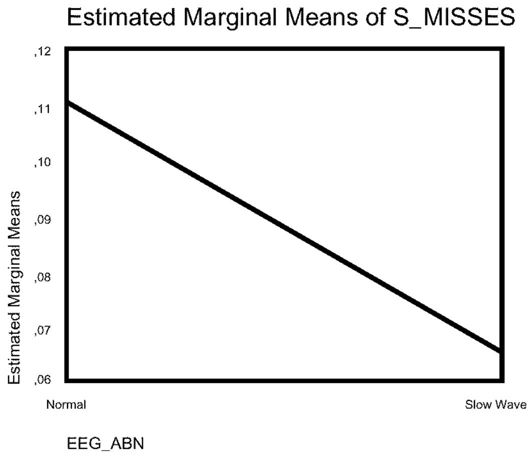
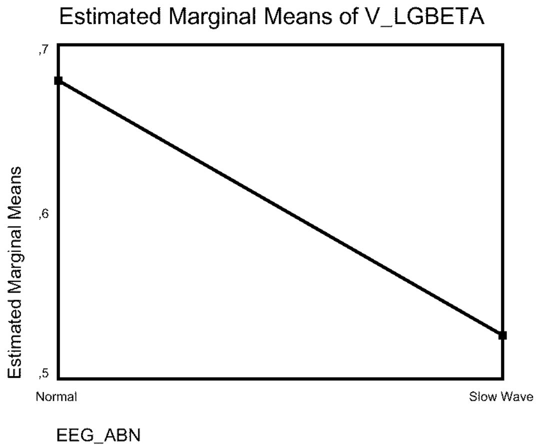


Fig.7



2) Auditory "OddBall" Task

We didn't find any significant effect of either hypoxia or presence of non- specific EEG abnormalities, or even of the interaction of these two factors (**Table 2**)

DISCUSSION

The salient finding of this study was that the focal or bilateral brief periods of slow activity in the EEG records of Hellenic air Force cadets combined with conditions of hypoxia did not affect their performance of the memory scanning tasks or their ERPs measured from the auditory "OddBall' task

The controversial results concerning the effect of EEG abnormality on the cognition tasks support the theory that the EEG slow activity is not predictive of a difference in cognitive function of Air Force cadets (17).

Cognitive function is an important component in the evaluation of pilot candidates. Our study will be fulfilled in about 2 years, when there will be a complete investigation whether there is an association between the scores of the aviation training and the scores of the cognitive tasks of the subjects who participated in this study.

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